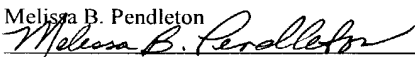
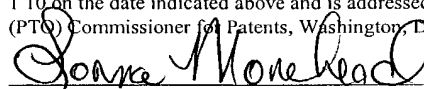


JC07 Rec'd PCT/PTO 28 FEB 2002

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|--|--|---|--|---|--|
| FORM PTO-1390 (REV 10-2000) | | U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE | | ATTORNEY'S DOCKET NUMBER 33339/244859 | |
| TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371 | | | | U.S. APPLICATION NO. (If known, see 37 C.F.R. 1.5) To be assigned 10/069913 | |
| INTERNATIONAL APPLICATION NO. PCT/FR00/02421 | | INTERNATIONAL FILING DATE September 1, 2000 | | PRIORITY DATE CLAIMED September 1, 1999 | |
| TITLE OF INVENTION Use Of A Low Molecular Weight Sulphated Polysaccharide To Obtain A Medicine With Antithrombotic Activity | | | | | |
| APPLICANT(S) FOR DO/EO/US Sylvia Collic-Jouault; Patrick Durand; Anne-Marie Fischer; Jacqueline Jozefonvicz; Didier Letourneur; Jean Millet | | | | | |
| Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information: | | | | | |
| 1. <input checked="" type="checkbox"/> This is a FIRST submission of items concerning a filing under 35 U.S.C. 371. 2. <input type="checkbox"/> This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. 371. 3. <input checked="" type="checkbox"/> This is an express request to promptly begin national examination procedures (35 U.S.C. 371(f)). 4. <input type="checkbox"/> The US has been elected by the expiration of 19 months from the priority date (PCT Article 31). 5. <input checked="" type="checkbox"/> A copy of the International Application as filed (35 U.S.C. 371(c)(2)) a. <input checked="" type="checkbox"/> is attached hereto (required only if not communicated by the International Bureau) b. <input type="checkbox"/> has been communicated by the International Bureau c. <input type="checkbox"/> is not required, as the application was filed in the United States Receiving Office (RO/US) 6. <input type="checkbox"/> A English language translation of the International Application as filed (35 U.S.C. 371(c)(2)) 7. <input checked="" type="checkbox"/> Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3)) a. <input type="checkbox"/> are attached hereto (required only if not communicated by the International Bureau). b. <input type="checkbox"/> have been communicated by the International Bureau. c. <input checked="" type="checkbox"/> have not been made; however, the time limit for making such amendments has NOT expired. d. <input type="checkbox"/> have not been made and will not be made 8. <input type="checkbox"/> An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)) 9. <input type="checkbox"/> An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)). 10. <input type="checkbox"/> An English language translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)) | | | | | |
| Items 11. To 16. Below concern other document(s) or information included: | | | | | |
| 11. <input type="checkbox"/> An Information Disclosure Statement under 37 C.F.R. 1.97 and 1.98. 12. <input type="checkbox"/> An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included. 13. <input type="checkbox"/> A FIRST preliminary amendment <input type="checkbox"/> A SECOND or SUBSEQUENT preliminary amendment. 14. <input type="checkbox"/> A substitute specification. 15. <input type="checkbox"/> A change of power of attorney and/or address letter. 16. <input type="checkbox"/> Other items or information. | | | | | |

JC19 Rec'd PCT/PTO 28 FEB 2002

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|---|--|--|---|------------------------------------|---------|
| U.S. APPLICATION NO (If known, see 37 CFR 1.50) To be assigned | | INTERNATIONAL APPLICATION NO PCT/FR00/02421 | | ATTORNEY'S DOCKET NUMBER 33339/ | |
| 17. <input checked="" type="checkbox"/> The following fees are submitted: | | | | CALCULATIONS | |
| Basic National Fee (37 CFR 1.492(a)(1)-(5)): Neither international preliminary examination fee (37 CFR 1.482) nor International search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO | | | | | |
| International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO | | | | \$ 890.00 | |
| International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search (37 CFR 1.445(a)(2)) paid to USPTO | | | | \$ 740.00 | |
| International preliminary examination fee (37 CFR 1.482) paid to USPTO But all claims did not satisfy provisions of PCT Article 33(1)-(4) | | | | \$ 710.00 | |
| International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4) | | | | \$ 100.00 | |
| ENTER APPROPRIATE BASIC FEE AMOUNT | | | | \$ 890.00 | |
| Surcharge of \$130.00 for furnishing the oath or declaration later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(e)). | | | | \$ | |
| CLAIMS | | NUMBER FILED | NUMBER EXTRA | RATE | |
| Total Claims | | 0 -20 = | 0 | X \$18.00 | \$ 0.00 |
| Independent Claims | | 0 - 3 = | 0 | X \$84.00 | \$ 0.00 |
| MULTIPLE DEPENDENT CLAIM(S) (if applicable) | | | | + \$280.00 | \$ |
| TOTAL OF ABOVE CALCULATIONS | | | | \$ | |
| <input type="checkbox"/> Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by one-half. | | | | \$ | |
| SUBTOTAL | | | | \$ | |
| Processing fee of \$130.00 for furnishing the English translation later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(f)). | | | | \$ | |
| TOTAL NATIONAL FEE | | | | \$ 890.00 | |
| Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). \$40.00 per property + | | | | \$ | |
| TOTAL FEES ENCLOSED | | | | \$ 890.00 | |
| | | | | Amount to be Refunded | |
| | | | | Charged | |
| a. <input checked="" type="checkbox"/> A check in the amount of \$ 890.00 to cover the above fees is enclosed. | | | | | |
| b. <input type="checkbox"/> Please charge my Deposit Account No. 16-0605 in the amount of \$ to cover the above fees. | | | | | |
| c. <input checked="" type="checkbox"/> A duplicate copy of this sheet is enclosed. | | | | | |
| The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 16-0605 | | | | | |
| Note: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137 (a) or (b)) must be filed and granted to restore the application to pending status. | | | | | |
| SEND ALL CORRESPONDENCE TO: Melissa B. Pendleton  SIGNATURE REGISTRATION NUMBER: 35,459 ALSTON & BIRD LLP Bank of America Plaza 101 South Tryon Street, Suite 4000 Charlotte, NC 28280-4000 Tel Charlotte Office (704) 444-1000 Fax Charlotte Office (704) 444-1111 Customer Number 00826 | | | "Express Mail" Mailing Label Number EL 822757615 US Date of Deposit: February 28, 2002 I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to BOX PCT, Attn DO/US (PTO) Commissioner for Patents, Washington, DC 20231  Lorna Morehead CLT01/4522100v1 | | |

WO 01/15654

PCT/FR00/02421

USE OF A LOW MOLECULAR WEIGHT SULFATED POLYSACCHARIDE
FOR PRODUCING A MEDICINAL PRODUCT WITH ACTIVITY AGAINST
VASCULAR THROMBOSIS

5 The present invention relates to the use of a sulfated
polysaccharide with a molar mass of less than or equal
to 10,000 g/mol, which can be obtained by radical
depolymerization of a crude fucan derived from
Phaeophyceae, for producing a medicinal product with
10 activity against arterial thrombosis and against
arterial restenosis.

Thrombosis consists of the formation of a clot
(*thrombus*) in the circulatory system, this clot
15 obstructing the lumen of the vessel in which it forms.
It is the consequence of the pathological activation of
the physiological phenomena of haemostasis, i.e. of the
phenomena which contribute to the prevention and arrest
of bleeding.

20 Thrombosis brings into a play a complex process
involving the activation, in cascade, of various
factors, resulting in the formation of thrombin, which
is a key clotting enzyme, and then in fibrin formation.
25 The formation of the *thrombus* begins with adhesion of
the platelets to the subendothelial connected tissue,
exposed by a lesion of the vascular endothelium. The
platelets aggregate with one another and the aggregate
becomes surrounded by a fibrin network which also traps
30 white blood cells and red blood cells, forming the
thrombus.

Arterial thrombosis differs from venous thrombosis in
that, most commonly, it occurs on an artery in which
35 there is a lesion due to the presence of an atheroma
plaque; this lesion is also characterized by the
proliferation and the migration toward the *intima* of
the smooth muscle cells of the *media*. Arterial
thrombosis often occurs when the atheroma plaque

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synthesized and are in particular marketed under the names Enoxaparin[®], Reviparin[®], Dalteparin[®], Fraxiparin[®], Tinzaparin[®], Certoparin[®], Opocrin[®], Parnaparin[®] etc.

5 Clinical studies have shown that the effectiveness of the LMWHs in the prophylaxis of venous thromboembolic accidents is identical to, if not greater than, that of NFH. However, the LMWHs do not abolish the hemorrhagic risk and can cause, just as NFH, although less
10 frequently, immunoallergic thrombopenia.

Furthermore, it has been shown, in particular by M. Lerch et al. (European Heart Journal, August 1998, 19, 495) and H. Rickli et al. (European Heart Journal,
15 August 1998, 19, 470), that LMWHs (Reviparin[®] and Fraxiparin[®] respectively) are ineffective in combating restenosis after angioplasty, i.e. the phenomenon of reappearance of a stricture of the lumen of an artery linked to the involvement of a balloon catheter in
20 vascular surgery.

Sulfated polysaccharides other than heparins exist, for example fucans. These sulfated polysaccharides, of high molecular weight (100 to 800 kDa), are present in the
25 cell walls of the thalli of brown algae. They are polymers of sulfated L-fucose and may also contain D-xylose, D-galactose, D-mannose and uronic acids, the latter not being sulfated, contrary to those of heparin. Fucans also differ from heparin in that they
30 do not comprise any amino sugars.

Fucans have various properties which make their use in many therapeutic domains particularly advantageous.

35 It has in particular been shown that fractions of low molar mass fucan, obtained by acid hydrolysis as described in European patent 0 403 377, have an anticoagulant (S. Colliec et al., Thromb. Res., 1991, 64, 143-154) and antithrombotic activity, when given

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intravenously (S. Mauray et al., Thrombosis and Haemostasis, 1995, 74(5), (280-1285) or subcutaneously (J. Millet et al., Thrombosis and Haemostasis, 1999, 81, 391-395) comparable to that of the low molecular
5 weight heparins.

It has also been shown that these same fucan fractions are capable of inhibiting, like heparin, the growth of vascular smooth muscle cells in culture (D. Logeart
10 et al., Eur. J. Cell. Biol., 1997, 74, 376-384 and 385-390). The effects observed are reversible, are not related to a cytotoxic action and depend on the concentration of the compound in the culture medium. This antiproliferative effect on the growth of smooth
15 muscle cells appears to be specific since, at these concentrations, no inhibition is observed on the growth of fibroblast lines, and these compounds are observed to be capable of potentiating endothelial cell growth in culture (J.L. Giraux et al., Eur. J. Cell. Biol.
20 1998, 77, 352-359).

Giraux et al. have shown, in Thromb. Haemost., 1998, 80, 692-695, that the same fucan fractions, obtained by acid hydrolysis according to the protocol described in
25 European patent 0 403 377, induce, *in vitro*, the release of TFPI (Tissue Factor Pathway Inhibitor) by human umbilical cord vein endothelial cells, this being an effect which may contribute to the antithrombotic action of these fucan fractions.

30

In addition, it has been shown, in Patent application EP 0 846 129, that fucan fractions, obtained by radical depolymerization of a fucan from Phaeophyceae in the presence of a metal catalyst and of hydrogen peroxide,
35 and having a molar mass of less than or equal to 10,000 g/mol, conserve, *in vitro*, the anticoagulant properties of crude fucan. Such fucan fragments, obtained by radical depolymerization of a high molecular weight fucan, are different, with respect to

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- not having the potential risk of viral contamination related to products of animal origin,
- making it possible to obtain prevention of arterial occlusion in the context of prevention of restenosis, in particular following an angioplasty.

The inventors have now shown that, unexpectedly, these aims are achieved by using a sulfated polysaccharide which can be obtained by radical depolymerization of a crude fucan derived from Phaeophyceae, said polysaccharide having a molar mass of less than or equal to 10,000 g/mol.

A subject of the present invention is the use of a sulfated polysaccharide which can be obtained by radical depolymerization of a crude fucan derived from Phaeophyceae, said polysaccharide having a molar mass of less than or equal to 10,000 g/mol, for producing a medicinal product intended to prevent or treat vascular thrombosis.

Particularly advantageously, the use of such a sulfated polysaccharide makes it possible to obtain an antithrombotic effect which is not accompanied by a major hemorrhagic risk.

Said sulfated polysaccharide can be obtained as described in Patent application EP 0 846 129. By way of example, the type of Phaeophyceae from which said sulfated polysaccharide is derived is *Ascophyllum nodosum*, *Fucus vesiculosus*, *Pelvetia canaliculata* or *Undaria pinnatifida*.

Particularly advantageously, the plant origin of the polysaccharide used in the present invention eliminates any risk of viral contamination of the individual to which it is administered.

According to an advantageous embodiment of the use according to the invention, said medicinal product is intended to prevent or treat venous thrombosis.

5 According to another advantageous embodiment of the use according to the invention, said medicinal product is intended to prevent or treat arterial thrombosis, a process in which the formation of the *thrombus* and the platelet deposits play an important role.

10

According to an advantageous arrangement of this embodiment, said medicinal product is intended to prevent arterial restenosis, a phenomenon which is a precursor to arterial thrombosis.

15

Specifically, in the context of the prevention of arterial thrombosis, it is particularly advantageous to seek to prevent arterial restenosis, this being a pathological condition which, when it manifests itself, may result in a thrombosis of the artery.

20

The sulfated polysaccharide used in the present invention advantageously has a molar mass of less than 5000 g/mol.

25

According to another advantageous embodiment of the present invention, said medicinal product is intended to be administered parenterally, preferably intravenously or subcutaneously.

30

In rabbits, in an experimental model of venous thrombosis, after subcutaneous injection, the same antithrombotic activity is observed for doses of LMWH and of sulfated polysaccharide (polysaccharide which can be obtained by radical depolymerization of a crude fucan derived from Phaeophyceae, as described above) equal to 1 mg/kg and to 10 mg/kg, respectively, i.e. for a dose of sulfated polysaccharide 10 times greater than that of an LMWH.

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following description, which refers to examples of measuring the antithrombotic activity, the hemorrhagic risk and the anticoagulant effect of sulfated polysaccharides obtained by depolymerization of a fucan from Phaeophyceae, and also to the study of the effects of these polysaccharides on platelet aggregation.

It should be clearly understood, however, that these examples are given only by way of illustration of the subject of the invention, of which they in no way constitute a limitation.

EXAMPLE 1: ANTITHROMBOTIC ACTIVITY OF SULFATED POLYSACCHARIDES OBTAINED BY DEPOLYMERIZATION OF A FUCAN FROM PHAEOPHYCEAE

1. Preparation of the low molecular weight fucan and of its references

In this example and in those which follow, unless otherwise indicated, the references for the low molecular weight fucan are as follows:

- the standard nonfractionated heparin (NFH) is a TERHORMON TH/023 heparin (150 IU/mg) supplied by Terdobliate (Novara, Italy). It has a mean molecular mass of approximately 15,000 g/mol;
- the low molecular weight heparin (LMWH) is supplied by Pharmacia (France) under the name Fragmine* (batch 94134, 2500 IU anti-Xa/0.2 ml). It has a mean molecular mass of approximately 5000 g/mol.

The required concentrations of NFH and of LMWH are obtained by dilution with physiological saline.

The low molecular weight fucan (LMWF) used is obtained by radical depolymerization of a fucan from

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Phaeophyceae (*Ascophyllum nodosum*) in accordance with the method described in Patent application EP 0 846 129. The protocol used is as follows:

5 - Radical depolymerization

25 liters of aqueous fucan extract, obtained according to the protocol described by Nishino et al. (Carbohydrate Research, 1989, 186, 119-129) adjusted
10 for the alga *Ascophyllum nodosum*, are introduced into a reactor with a volume of 45 liters, equipped with a device for stirring at 100 rpm. The temperature is brought to and maintained at 60°C. 75 g of copper acetate (Fluka) are added, i.e. a copper acetate
15 concentration of 0.02 M. The pH is adjusted to 7.5 with approximately 400 ml of 2 N sodium hydroxide (NaOH 400 g/l, Panréac). Hydrogen peroxide is then added at a concentration of 10 to 13% at a flow rate of 85 ml/minute, for 4 h.

20

- Removal of the copper

The reaction medium is filtered over glass microfiber filters, the pore diameter of which is 2.6 µm (Whatman
25 filters, reference GF/D 1823-150), in order to remove the green-colored precipitate formed during the depolymerization reaction. The residual copper is then retained by passage over a resin (Chelex® 20, Biorad): the depolymerized extract is introduced, at a flow rate
30 of 13 to 15 l/h, into a glass column, with a cross section of 113 cm², containing 5 liters of pre-passivated resin. The solution of depolymerized fucan leaving the column is decolorized and has a pH of between 10 and 11.

35

The resin used is then regenerated according to the operating conditions given by the manufacturer.

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- Diafiltration, concentration and lyophilization

The solution of depolymerized fucan obtained above is subjected to ultrafiltration on a Pellicon® (Millipore) system equipped with two 1 kDalton polysulfone membranes (Filtron). Conductivity is monitored throughout this process, using 10 volumes of osmosed water.

After having been concentrated down to a final volume of 4 to 5 liters, the product is lyophilized. The yield, calculated on the lyophilizate, is 27%.

- Reduction with borohydride

267 g of the depolymerized fucan obtained above (lyophilized fucan) are dissolved in 3 l of osmosed water and the solution is homogenized. 10 ml of this solution are taken for analysis of the fucan before the step of reduction of the terminal monosaccharides of the polysaccharide chains.

Separately, 202 g of sodium borohydride are dissolved in 3 l of water. The borohydride solution is then added to the fucan solution. The reaction is immediate and very effervescent. After 2 hours, the reaction is stopped by adding 10 N acetic acid (glacial acetic acid, Panréac) until a neutral pH is obtained. The volume of acid added is 400 ml.

After neutralization, the solution is filtered over glass microfibers (Whatman filter, reference GF/D 1822-290) and subjected to ultrafiltration/diafiltration on a Pellicon® system (Millipore) equipped with two polysulfone membranes with a cut-off threshold of 1 kDalton (Filtron). The initial volume is 9 l; the initial conductivity is 16.5 mS and falls to 3.5 mS at the end of the ultrafiltration/diafiltration. After concentrating down to 7.5 l, the product is successively filtered over filters with pore diameters

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Results

The LMWF has a dose-dependent activity which manifests itself from a dose of 2.5 mg/kg, with a significant decrease in the weight of the thrombi of close to 35%. This activity is close to 100% for a dose of 10 mg/kg.

Activities of 50%, 80% and 90% were obtained for respective doses of Fragmin® of 80, 100 and 200 IU anti-Xa/kg (Millet et al., 1999, *ibid.*).

Mathematical calculation, using a logarithmic regression, makes it possible to determine the dose of LMWF required to decrease the weight of the control thrombi by 80% (ED 80). Thus, the ED 80 for the LMWF, given subcutaneously, is 7.4 (5.6-9.8) mg/kg.

As observed by Millet et al., 1999 (*ibid*) on the low molecular weight fucan obtained by acid hydrolysis, and taking Fragmin® as the reference product, the LMWF shows, in rabbits, earlier and longer-lasting kinetics of antithrombotic activity.

3. Arteriovenous thrombosis according to Umetsu in rabbits

3-a: Antithrombotic activity intravenously

• Protocol

The animals used are homozygous New Zealand male rabbits weighing on average 2 to 2.5 kg. After a 6-day period of stabilization of the animals in an animal house, they are used during a period of fasting.

After premedication of the animals with Imalgene®, they are anesthetized by intravenous injection of 1% sodium pentobarbital into the marginal ear vein. The injection is given slowly with the pupil reflex and respiration

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being monitored. Approximately 4 to 5 ml of pentobarbital are injected into a rabbit weighing 2 kg.

A carotid artery and an opposite jugular vein are freed. An arteriovenous shunt is placed between these two vessels. This shunt is composed of 2 polyethylene catheters (outside diameter 1.9 mm) 12.5 cm in length, these two catheters being connected to one another via a third catheter, which has an internal diameter of 1.57 mm and is 6 cm in length, inside which is placed a silk thread.

The catheters are siliconized (Sigmacote[®], Sigma). A Doppler ring 1.3 mm in diameter is fixed around the catheter introduced into the carotid in order to assess the variation in blood flow velocity, representative of the occlusion.

A first group of rabbits, which will be used as a control, receives physiological saline, three other groups receiving, respectively, a solution of NFH (1 mg/kg) and two solutions of LMWF (1 mg/kg and 2 mg/kg). The various solutions and their solvents (the physiological saline) are administered in a volume of 1 ml/kg, by intravenous injection into a marginal ear vein (on the opposite side to that being used to maintain the anesthesia of the animal), 5 minutes before creating the thrombogenic situation.

• Results

Table II summarizes the occlusion times (in minutes) as a function of the doses of LMWF and of NFH administered intravenously. The symbol *** indicates the threshold of significance of a probability equal to or less than 0.1% ($p \leq 0.001$ in the statistical Student's test).

Table II

| | Control | NFH 1 mg/kg | LMWF | |
|-----------------------|------------|---------------|------------|---------------|
| | | | 1 mg/kg | 2 mg/kg |
| Occlusion time (min.) | 15.6 ± 1.7 | 55.4 ± 2.9*** | 27.6 ± 6.5 | 43.7 ± 6.0*** |
| Number of animals | 9 | 5 | 7 | 6 |

It emerges from these results that the LMWF, administered intravenously in the Umetsu model adapted to rabbits, has arterial antithrombotic activity at doses close to those responsible for venous antithrombotic activity.

Doubling of the occlusion time is noted 5 minutes after intravenous administration of LMWF at a dose of 1 mg/kg (dose close to the venous antithrombotic ED 80). The NFH administered at a dose of 1 mg/kg, under the same conditions, increases close to 4-fold the time required to obtain complete vascular obstruction in the control animals. Moreover, it should be noted that this dose corresponds to 10 times the venous antithrombotic ED 80 for the NFH.

3-b: Antithrombotic activity subcutaneously

• Protocol

The protocol as indicated above is carried out, the various solutions and their solvents (the physiological saline) being administered in a volume of 1 ml/kg, subcutaneously, 2 hours being creating the thrombogenic situation. The animals are divided into three groups: a first group, which will be used as a control, receives physiological saline, whereas the other groups receive, respectively, solutions of LMWF at a dose of 7.5 mg/kg and of LMWH at a dose of 60 IU anti-Xa/kg.

• Results

Table III summarizes the occlusion times (in minutes) as a function of the doses of LMWF and of LMWH administered subcutaneously.

Table III

| | Control | LMWH (60 IU anti-Xa/kg) | LMWF (7.5 mg/kg) |
|--------------------------|------------|-------------------------------|---------------------|
| Occlusion time (min.) | 12.6 ± 1.0 | 11.8 ± 1.3 | 22.8 ± 3.4 |
| Number of animals | 5 | 4 | 4 |

It emerges from these results that, at the doses tested, given subcutaneously, the LMWF doubles the control occlusion time, whereas the LMWH has no effect.

Contrary to that which is noted for the NFH (by intravenous injection) and for the LMWH (subcutaneous injection), the dose of LMWF required to double the arterial occlusion time is very close to the venous antithrombotic ED 80 (namely 7.4 mg/kg), unlike the heparins, for which it is necessary to multiply the venous antithrombotic dose close to 10-fold in order to obtain a dose which is active in arterial thrombosis.

4. Arterial thrombosis with FeCl₃ in rats

• Protocol

Only intravenous administration was studied in this model.

The animals used are male Wistar rats weighing from 240 to 390 g. After a 6-day period of stabilization of the

animals in an animal house, they are used in a period of fasting.

After anesthesia with 15% ethyl carbonate (10 ml/kg; Prolabo, Paris, France), a carotid artery is exposed and surrounding tissues or nerves are cleared, and a square of parafilm is placed under the carotid. A Doppler probe is placed around the carotid (cephalic side). The Doppler signal is adjusted so as to have a deflection which is maximal and assimilated to a value of 100%.

After a period of stabilization of the blood flow, a disc (3 mm in diameter) of Whatman filter paper is placed on the carotid, distally to the probe. Two microliters of a solution of FeCl_3 (Osi, Paris, France) at 25% in 1 M hydrochloric acid are deposited on to the filter paper, which is then placed vertically to the parafilm in contact with the cleared carotid. A timer is started. After 30-second contact of the filter paper, this is removed. The formation the *thrombus* is then monitored by analyzing the Doppler signal.

Evaluation of the thrombosis, expressed in minutes, consists in measuring the period of time which separates the application of the FeCl_3 from the time at which the Doppler signal reaches the base line, thus reflecting total occlusion.

The animals are divided up into three main groups, one receiving the physiological saline (control group) and the others receiving, respectively, the LMWF (at doses ranging from 1.25 to 10 mg/kg) and the NFH (at the doses of 1.25 and 2.5 mg/kg). The physiological saline, and also the solutions of LMWF and of NFH, are injected intravenously, in a volume of 1 ml/kg, 5 minutes before inducing the thrombosis.

• Results

Table IV summarizes the arterial occlusion times (in minutes) and also the multiplication factor for the occlusion time (calculated relative to the control occlusion time), as a function of the doses of LMWF and of NFH administered intravenously. The symbols *** and ** indicate the thresholds of significance of a probability equal to or less than 0.1% and 1%, respectively ($p \leq 0.001$ and $p \leq 0.1$, respectively, in the statistical Student's test).

Table IV

| | Occlusion time (min.) | Multiplication factor | Number of animals |
|------------|-----------------------|-----------------------|-------------------|
| Control | 11.6 \pm 0.58 | / | 19 |
| LMWF: | | | |
| 10 mg/kg | 52.5 \pm 7.5*** | 4.52 | 6 |
| 5 mg/kg | 41.7 \pm 8.9*** | 3.59 | 7 |
| 2.5 mg/kg | 31.9 \pm 9.3** | 2.75 | 6 |
| 1.25 mg/kg | 12.7 \pm 1.4 | 1.09 | 5 |
| NFH: | | | |
| 2.5 mg/kg | 60.0 \pm 0*** | 5.17 | 2 |
| 1.25 mg/kg | 20.5 \pm 0.5** | 1.76 | 3 |

As shown in the table above, the occlusion time is 20.5 minutes after an injection of NFH at a dose of 1.25 mg/kg and 60 minutes when the NFH is administered at a dose of 2.5 mg/kg, i.e. more than 5 times the control time.

With regard to the LMWF, it has a significant dose-dependent activity. From the dose of 2.5 mg/kg, the injection of LMWF induces a significant delay in the arterial occlusion time, this time being more than doubled compared to the control time.

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LMWH is inactive in rabbits in the model of arterial thrombosis according to the Umetsu model.

At 5 times this dose, neither the LMWH or the LMWF induces a significant increase in the bleeding time.

2. Hemorrhagic risk in rats

a) Materials and methods

10

In rats, the hemorrhagic risk of the LMWF, of the NFH and of the LMWH is evaluated by measuring the increase in the bleeding times, according to the model of Dejana et al. (Throm. Haemost., 1982, 48, 108-111). The LMWF, the NFH and the animals used are identical to those described in Example 1.

The compounds are administered intravenously at doses of 5 and 10 mg/kg for the LMWF (doses corresponding, respectively, to 2.5 times and to 5 times the dose which doubles the control occlusion time (OT) (cf. Table IV), of 750 and 1500 IU anti-Xa/kg for the LMWH (Fragmin®) and of 1 mg/kg for the NFH, 5 minutes before induction of the hemorrhage.

25

b) Results

Table V summarizes, as percentages, the increase in the bleeding times obtained.

30

Table V

| Doses | Products | Increase in the bleeding times | Number of animals |
|--------------|----------|--------------------------------|-------------------|
| 1 X OT X 2 | LMWF | nd* | 9 |
| | NFH | >80% | |
| 2.5 X OT X 2 | LMWF | >50% | 8 |
| | LMWH | >200% | 8 |
| 5 X OT X 2 | LMWF | >200% | 3 |

- 25 -

(administration of the compounds intravenously)

In rats, intravenous injection of LMWF significantly prolongs the APTT and the TT, but clearly less than
5 that which is observed with the NFH.

- Anticoagulant effect in rabbits

(administration of the compounds subcutaneously)

10 The results of the KCTs obtained in rabbits, expressed in seconds, are summarized in Table VI below. The symbols * and ** indicate the thresholds of significance of a probability equal to or less than 5% and 1%, respectively ($p \leq 0.05$ and $p \leq 0.01$, respectively, in
15 the statistical Student's test).

Table VI

| | Dose | KCT (seconds) | Number of animals |
|---------|-------------------|------------------|-------------------|
| Control | 0 | 25.1 \pm 1.3 | 8 |
| LMWF | 7.5 mg/kg | 28.2 \pm 1.8 | 6 |
| | 10 mg/kg | 29.4 \pm 1.5* | 7 |
| LMWH | 50 IU anti-Xa/kg | 25.7 \pm 1.7 | 3 |
| | 100 IU anti-Xa/kg | 27.0 \pm 1.5 | 3 |
| | 200 IU anti-Xa/kg | 33.9 \pm 5.0** | 3 |

20 It emerges from Table VI that the LMWH (Fragmin[®]), administered at doses ranging from 50 to 200 IU anti-Xa/kg, 2 hours before the blood samples are taken, does not a significant increase in the KCT except at a very high dose (200 IU anti-Xa/kg) (35.3% increase
25 compared to the control group).

The KCT undergoes no significant modification for a dose of LMWF of 7.5 mg/kg, administered subcutaneously 2 hours before the blood samples are taken. At a dose
30 of 10 mg/kg, a slight but significant increase is noted (17% increase).

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The results of the TTs obtained in rabbits, expressed in seconds, are summarized in Table VII below. The symbol ** indicates the threshold of significance of a probability equal to or less than 1% ($p \leq 0.01$ in the statistical Student's test).

Table VII

| | Dose | TT (seconds) | Number of animals |
|---------|-------------------|----------------|-------------------|
| Control | 0 | 31.6 ± 1.3 | 9 |
| LMWF | 7.5 mg/kg | 34.7 ± 2.2 | 6 |
| | 10 mg/kg | 31.5 ± 1.2 | 7 |
| LMWH | 50 IU anti-Xa/kg | 32.5 ± 2.7 | 3 |
| | 100 IU anti-Xa/kg | 38.2 ± 4.1 | 3 |
| | 200 IU anti-Xa/kg | $> 98^{**}$ | 3 |

It emerges from Table VII that the mean thrombin time (TT) undergoes no significant modification for the doses of LMWF tested, administered subcutaneously 2 hours before the blood samples are taken. It is noted that the LMWH (Fragmin®), at the doses tested, increases the TT.

EXAMPLE 3: EX VIVO STUDY OF THE EFFECT OF SULFATED POLYSACCHARIDES OBTAINED BY RADICAL DEPOLYMERIZATION OF A FUCAN FROM PHAEOPHYCEAE ON PLATELET AGGREGATION

a) Materials and methods

The LMWF and the NFH are as described in Example 1. The LMWH is Tinzaparin®, supplied by Innohep.

• In rabbits

The LMWF and the LMWH are injected, subcutaneously, at a dose close to 5 x ED 80 (5 times the dose required to decrease the mean weight of the control thrombi by 80%) determined according to the venous thrombosis model

The platelet aggregation protocols are similar to those described above, except for the following differences for the protocol for aggregation with thrombin: the buffer added to the PRP is a recalcified Tyrode's
 5 buffer, and the final concentration of thrombin is 0.6 U NIH/ml.

b) Results

10 • In rabbits

The LMWF and the LMWH (at the dose of 5 x ED 80) and the NFH (at the dose of 10 x ED 80) inhibit the thrombin-induced platelet aggregation at 100%, but do
 15 not inhibit the platelet aggregation induced with 1 μ M and 2 μ M of ADP.

• In rats

20 The LMWF and the NFH inhibit the thrombin-induced platelet aggregation at 100%.

Contrary to that which is noted following the injection of NFH (lack of inhibition or very weak inhibition of
 25 platelet aggregation), the LMWF, whatever the dose injected, decreases the ADP-induced platelet aggregation by 35 to 45%, without it being possible to observe a dose-effect.

30 **EXAMPLE 4: IN VIVO STUDY OF THE EFFECT OF SULFATED POLYSACCHARIDES OBTAINED BY RADICAL DEPOLYMERIZATION OF A FUCAN FROM PHAEOPHYCEAE ON THE PREVENTION OF ARTERIAL RESTENOSIS**

35 The treatment of arterial stenoses via the endovascular route is a technique which is common practice. It consists in introducing into the artery a balloon which is expanded against the stenosis (angioplasty operation) with the aim of restoring a normal vascular

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caliber. The angioplasty is most commonly followed by the insertion of a stent which makes it possible, due to its radial expansion strength, to maintain the caliber of the artery. This technique is frequently
 5 used in the treatment of coronary, iliac or renal atheromatous stenoses. The parietal trauma induced by the angioplasty and the insertion of a stent is, unfortunately, responsible for a restenosis of the vessel in 20 to 30% of cases in humans. This restenosis
 10 is largely due to proliferation and migration of the smooth muscle cells (SMCs) from the *media* to the *intima* of the vessel. The appearance of neointimal hyperplasia reduces the caliber of the stent, promotes downstream ischemia and is the cause, in humans, of not
 15 insignificant morbidity and mortality.

Fractions of sulfated polysaccharide which can be obtained by radical depolymerization of a crude fucan derived from Phaeophyceae, said polysaccharide having a
 20 molar mass of less than or equal to 10,000 g/mol, may be used, in accordance with the invention, to prevent arterial restenosis, as demonstrated below in a model of restenosis in rabbits, in the iliac artery.

25 a) Materials and methods

The animals are New Zealand rabbits weighing on average 3.5 to 4 kg. They are anesthetized with pentobarbital.
 30 10 iliac stents are implanted in 5 rabbits. A stent is positioned in each iliac artery (approach via the carotid). The insertion of each stent is preceded by 3 angioplasties of one minute at 10 atmospheres (atm). The stent is inserted under a pressure of 10 atm for
 35 30 seconds.

The animals are then treated for 14 days with the LMWF obtained in Example 1, injected intramuscularly twice a

day at the dose of 10 mg/kg/24 h. The control group consists of 6 stented arteries in 3 rabbits.

After 14 days, the animals are sacrificed. The lower
5 abdominal aorta and the iliac arteries are removed and
are fixed under pressure (in formol) and embedded in
methacrylate. Sections are then cut on a microtome in
order to carry out histological and histomorphometric
analyses, and to calculate the surface area of the
10 arteries.

b) Results

The surface area measurements carried out (*intima*,
15 *media*, and *intima/media* and *intima/internal* elastic
lamina ratios), given in Table VIII (in which "n"
represents the number of measurements made), indicate a
decrease in the intimal hyperplasia in the group of
animals treated with the LMWF. This decrease in the
20 intimal hyperplasia is very large (about 60%).

It should also be noted that, beyond the decrease in
the surface area of the *intima* and in the *intima/media*
and *intima/internal* elastic lamina ratios, the fucan
25 has no effect on the surface area of the *media*, which
reveals an inhibition specific for the SMC
proliferation.

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Table VIII

| | Control (n = 6) | Animals treated with the LMWF (n = 10) | Decrease (%) |
|-----------------------------|--------------------|--|--------------|
| <i>Intima</i> s.d. | 1.83 0.51 | 0.73 0.20 | 60 |
| <i>Media</i> s.d. | 0.41 0.02 | 0.37 0.19 | n.s. |
| <i>Intima/media</i> s.d. | 4.48 1.47 | 1.97 0.65 | 56 |
| <i>Intima/IEL</i> s.d. | 0.35 0.08 | 0.17 0.06 | 52 |

s.d. = standard deviation

5 n.s. = not significant

IEL = internal elastic lamina

As emerges from the above, the invention is in no way limited to its methods of implementation, preparation and application which have just been described more explicitly; on the contrary, it encompasses all the variants which may occur to a person skilled in the art, without departing from the context or scope of the present invention.

10

CLAIMS

1. The use of a sulfated polysaccharide which can be obtained by radical depolymerization of a crude fucan derived from Phaeophyceae, said polysaccharide having a molar mass of less than or equal to 10,000 g/mol, for producing a medicinal product intended to prevent or treat vascular thrombosis.
2. The use as claimed in claim 1, characterized in that said medicinal product is intended to prevent or treat venous thrombosis.
3. The use as claimed in claim 1, characterized in that said medicinal product is intended to prevent or treat arterial thrombosis.
4. The use as claimed in claim 3, for preventing arterial restenosis.
5. The use as claimed in any one of claims 1 to 4, characterized in that said sulfated polysaccharide has a molar mass of less than 5000 g/mol.
6. The use as claimed in any one of claims 1 to 5, characterized in that said medicinal product is intended to be administered parenterally.
7. The use as claimed in claim 6, characterized in that said medicinal product is intended to be administered intravenously.
8. The use as claimed in claim 6, characterized in that said medicinal product is intended to be administered subcutaneously.

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9. The use as claimed in claim 8, characterized in that said medicinal product is intended to be administered, preventatively, at a daily dose of between 150 and 300 mg.
- 5 10. The use as claimed in claim 8, characterized in that said medicinal product is intended to be administered, curatively, at a daily dose of between 450 and 600 mg.
- 10 11. The use as claimed in claim 4, characterized in that said medicinal product is intended to be administered locally.
- 15 12. The use as claimed in claim 11, characterized in that said medicinal product is intended to be administered by endoparietal diffusion.

5

The invention concerns the use of a sulphated polysaccharide capable of being obtained by radical depolymerization of a raw fucan derived from Pheophyceae, said polysaccharide having a molar mass not more than 10.000 g/mol, to obtain a medicine for preventing or treating vascular thrombosis, in particular venous thrombosis, arterial thrombosis and arterial restenosis.

Declaration and Power of Attorney for Patent Application
Déclaration et Pouvoirs pour Demande de Brevet
French Language Declaration

En tant l'inventeur nommé ci-après, je déclare par le présent acte que :

Mon domicile, mon adresse postale et ma nationalité sont ceux figurant ci-dessous à côté de mon nom.

Je crois être le premier inventeur original et unique (si un seul nom est mentionné ci-dessous), ou l'un des premiers co-inventeurs originaux (si plusieurs noms sont mentionnés ci-dessous) de l'objet revendiqué, pour lequel une demande de brevet a été déposée concernant l'invention intitulée

et dont la description est fournie ci-joint à moins

- ☐ ci-joint
☐ a été déposée le

sous le numéro de demande des
Etats-Unis ou le numéro de demande
international PCT

et modifiée le
(le cas échéant).

Je déclare par le présent acte avoir passé en revue et compris le contenu de la description ci-dessus, revendications comprises, telles que modifiées par toute modification dont il aura été fait références ci-dessus.

Je reconnais devoir divulguer toute information pertinente à la brevetabilité, comme défini dans le Titre 37, § 1.56 du Code fédéral des réglementations.

As a below named inventor, I hereby declare that :

My residence, post office address and citizenship are as stated next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed an for which a patent is sought on the invention entitled

**USE OF A LOW MOLECULAR WEIGHT
SULPHATED POLYSACCHARIDE TO
OBTAIN A MEDICINE WITH
ANTITHROMBOTIC ACTIVITY**

the specification of which :

- ☐ is attached hereto.
☒ was filed on **February 28, 2002**

as United States Application Number
No. 10/069,913 or
PCT International Application Number

and was amended on
(if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, § 1.56.

French Language Declaration

Je revendique par le présent acte avoir la priorité étrangère, en vertu du Titre 35, § 119(a)-(d) ou § 365(b) du Code des Etats-Unis, sur toute demande étrangère de brevet ou certificat d'inventeur ou, en vertu du Titre 35, § 365(a) du même Code, sur toute demande internationale PCT désignant au moins un pays autre que les Etats-Unis et figurant ci-dessous et, en cochant la case, j'ai aussi indiqué ci-dessous toute demande étrangère de brevet, tout certificat d'inventeur ou toute demande internationale PCT ayant date de dépôt précédant celle de la demande à propos de laquelle une priorité est revendiquée.

Prior Foreign application(s)
Demande(s) de brevet antérieure(s) dans un autre pays.
99/10965 France

(Number) (Country)
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(Application No.) (Filing Date)
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(Application No.) (Filing Date)
(N° de demande) (Date de dépôt)

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(N° de demande) (Date de dépôt)

Je déclare que par le présent acte que toute déclaration ci-incluse est, à ma connaissance, véridique et que toute déclaration formulée à partir de renseignements ou de suppositions est tenue pour véridique ; et de plus, que toutes ces déclarations ont été formulées en sachant que toute fausse déclaration volontaire ou son équivalent est passible d'une amende ou d'une incarcération, ou des deux, en vertu de la section 1001 du Titre 18 du Code de Etats-Unis, et que de telles déclarations volontairement fausses risquent de compromettre la validité de la demande de brevet ou du brevet délivré à partir de celle-ci.

I hereby claim foreign priority under Title 35, United States Code, § 119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate, or § 365(a) of any PCT International application which designated at least one country other than the United States, listed below, and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or PCT International application having a filing date before that of the application on which priority is claimed.

Priority claimed
Droit de priorité
revendiqué

September 1st, 1999

(Day/Month/Year Filed) ☒ ☐
(Jour/Mois/Anné de dépôt) Yes No
Oui Non

(Day/Month/Year Filed) ☐ ☐
(Jour/Mois/Anné de dépôt) Yes No
Oui Non

I hereby claim the benefit under Title 35, United States Code, § 119(e) of any United States provisional application(s) listed below.

(Application No.) (Filing Date)
(N° de demande) (Date de dépôt)

I hereby claim the benefit under Title 35, United States Code, § 120 of any United States application(s), or § 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of Title 35, United States Code, § 112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, § 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

(Status) (patented, pending, abandoned)
(Statut) (breveté, en cours d'examen, abandonné)

(Status) (patented, pending, abandoned)
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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true ; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

French Language Declaration

POUVOIRS : En tant que l'inventeur cité, je désigne par la présente l'(les) avocats(s) et/ou agent(s) suivant(s) pour qu'ils poursuive(nt) la procédure de cette demande de brevet et traite(nt) toute affaire s'y rapportant avec l'Office des brevets et des marques : (mentionner le nom et le numéro d'enregistrement).

POWER OF ATTORNEY : As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to persecute this application and transact all business in the Patent and Trademark Office connected therewith : (list name and registration number)

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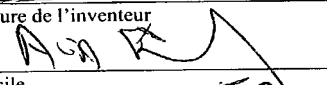
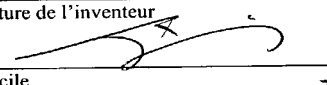
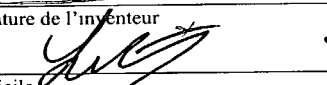
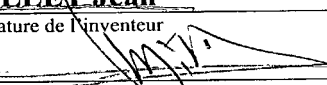
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|---|--|
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(Fournir les mêmes renseignements et la signature de tout co-inventeur supplémentaire.)

(Supply similar information and signature for third and subsequent joint inventors.)

French Language Declaration

| | |
|--|--|
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(Fournir les mêmes renseignements et la signature de tout co-inventeur supplémentaire.)

Supply similar information and signature for third and subsequent joint inventors.)